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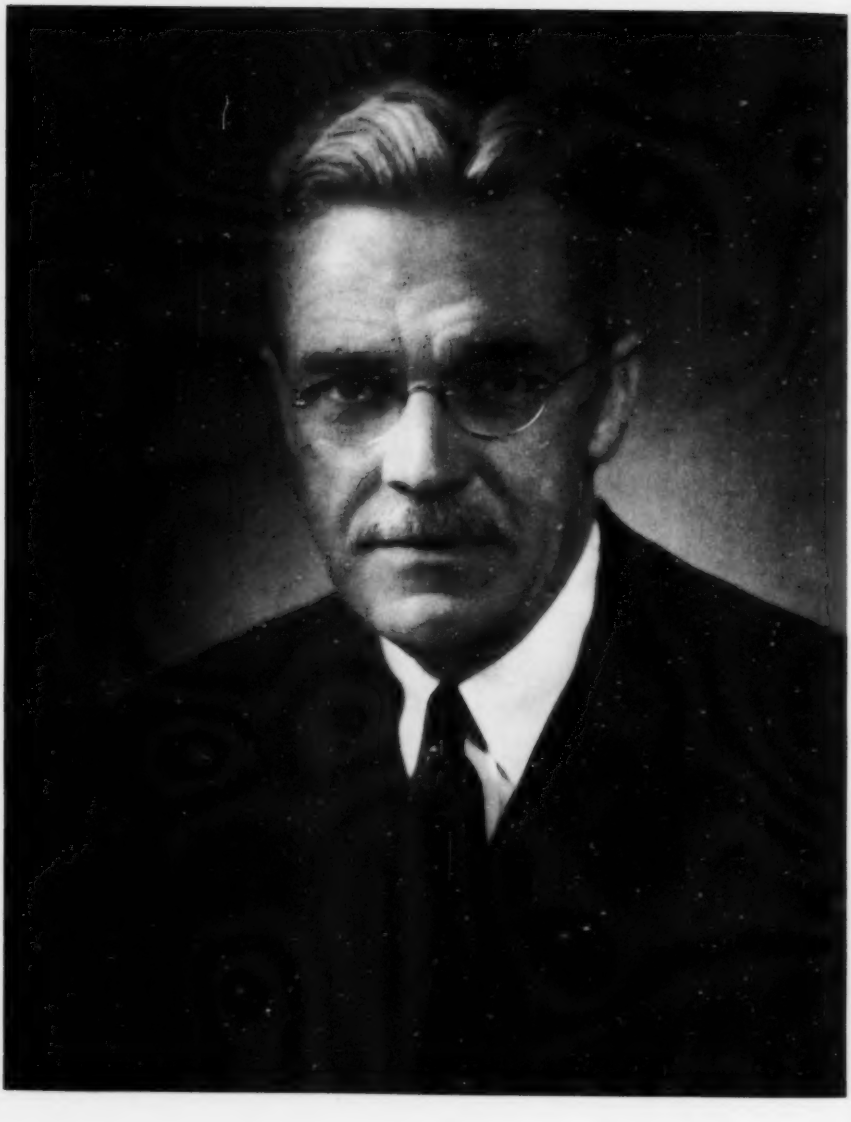

EDWARD M. HANRAHAN

1892–1952

The passing of Dr. Edward M. Hanrahan on September 30, 1952, brought mourning to the entire university community and saddened friends, patients and physicians throughout the United States. He had been the uncomplaining victim of poor health for many years but always cheerful and courageous up until the hour of his sudden death. His death has left a great void since his spirit, ideals and attitude were of profound influence not only in the department of surgery but also in the community.

Dr. Hanrahan was born in Binghamton, N. Y., the son of Edward M. and Julia Stack Hanrahan. After receiving his preliminary education in local schools he entered Cornell University in 1911, from which institution he was graduated in 1915. While attending Cornell University he received his premedical education, and was active socially and athletically. He was a member of the varsity track squad, where he excelled in the low hurdles. He was a member of the Alpha Delta Phi Fraternity and took unusual interest in the cultural development of the younger members of this society. In the fall of 1915 he entered The Johns Hopkins School of Medicine from which he was graduated in 1919. Following his first year in the medical school he spent his summer vacation working in one of the Grenfell Mission Hospitals at Battle Harbor on the Laborador Coast. There he met and formed a lasting friendship with Sir Wilfred Grenfell. After graduation Dr. Hanrahan was appointed to an internship on the surgical service of Dr. William S. Halsted. In the early spring of 1920 he developed a pleurisy with effusion and was hospitalized for a short period. This episode was undoubtedly tuberculous in origin although not recognized at the time. In the year previous to this attack Dr. Hanrahan had been very active in all forms of outdoor sports, having always enjoyed excellent health, but as the years went by he was forced to curtail his activities which was a great disappointment to him. He continued his surgical training, spending a year in surgical pathology in The Johns Hopkins Hospital followed by one year as an assistant resident on the service of Dr. J. M. T. Finney, Sr., at the Union Protestant Infirmary. As an assistant the following year on the surgical service of Professor Finsterer at the Allgemeines Krankenhaus in Vienna, he became interested in the use of local anaesthesia. On his return to Baltimore he entered the practice of general surgery.

In 1923 he married Evelyn Randall, of Baltimore, and to this marriage there were two children born, Edward M., III and Julia.

After some years in the practice of general surgery it became obvious that Dr. Hanrahan's health was failing and in 1933 a positive diagnosis of pulmonary tuberculosis was made. A series of rest periods in Trudeau Sanatorium

interfered with his surgical activities for the time being but afforded an opportunity for him to indulge his natural artistic talents. As a result he became interested in the production of *bas relief* portraits in bronze, and his study of Dr. Lewellys Barker now adorns the main corridor in The Johns Hopkins Hospital. Because of his excellent surgical technique combined with his keen artistic sense he limited his activities to plastic surgery, admirably suited to his talents. In this field he was eminently successful and organized, under the direction of Dr. Blalock, a department of plastic surgery. To the success of this department and to the training of the younger men he devoted his entire time and strength.

His loyalty to The Johns Hopkins School of Medicine was unswerving and in the conscientious devotion to the students, his patients and his profession lay the foundation of his fatal and final illness. He truly dedicated his life to the advancement of medical practice and education.

Wm. Francis Rienhoff, Jr.

SKELETAL CHANGES ASSOCIATED WITH HYPERTHYROIDISM

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That the thyroid gland plays an important role in maintaining the integrity of skeletal tissues cannot be questioned. In the hypothyroid state clinical, roentgenological, metabolic, and anatomical evidences of disturbances in the skeletal system are familiar enough. In the hyperthyroid individual skeletal disease has been noted clinically, by x-ray examination and by studies of calcium and phosphorus metabolism. However, very little attention has been directed to a microscopic examination of the bones of patients coming to autopsy with or without the history of medically and/or surgically treated hyperthyroidism. It is for this reason that the following observations are being presented.

Sections of vertebral bodies partially decalcified and embedded in nitrocellulose have been available for study from a group of 20 patients coming to autopsy at the Johns Hopkins Hospital during the period 1924–1952. Unfortunately, roentgenological examinations were not routinely carried out. Nor is information available with relation to serum concentrations of calcium or phosphorus. The only points for correlation are the clinical duration and severity of the disease and the period of therapy, if any, before death together with the response to medication.

Microscopic examination of the skeletal tissues reveals 3 different alterations: 1) *Osteitis fibrosa* or evidence of excessive destruction, 2) *Osteomalacia* or the defective deposition of inorganic elements in bone matrix (osteoid), and 3) *Osteoporosis* or general rarefaction.

Osteitis fibrosa: By "osteitis fibrosa" we mean changes, to be described below, which are taken to be indicative of excess destructive activity of varying degree. As we have pointed out elsewhere (1, 2) the term "osteitis fibrosa" has come to have a much wider meaning than the one which had previously been restricted to the bony changes which may be encountered in certain cases of primary hyperparathyroidism.

Evidence of excess destruction in varying degrees was found in all of the 20 cases studied. The extent has been arbitrarily graded from one to four plus and examples are shown in Figures 1 to 15 and 22. Several aspects deserve comment. The most common alteration is the presence of multiple small eroded areas along one or the other surface of a trabecula. Such irregularities give the affected edge a "saw-tooth" appearance. In the depressions between the projecting "teeth" cells are usually found. Sometimes such cells have a stellate

form and are clearly osteocytes which are being denuded by the partial disappearance of bone which has previously completely encased them. Other cells having more voluminous cytoplasm and larger nuclei resembling osteoblasts lie in small lacunae which they appear to have eroded. It is of interest that these "saw-tooth" areas may be found along only one surface of a trabecula and in localized foci. There may or may not be a proliferation of connective tissue cells in their vicinity. Associated with the mononuclear cells (osteoblasts) there may be multi-nucleated cells or osteoclasts. The spaces along the bony trabeculae in which these latter cells lie are large; more connective tissue cells are found in their vicinity.

In addition to the "saw-tooth" eroded lesions, which are found in all the cases in this series, areas indicative of more marked destructive activity are present in some. Such lesions consist of larger defects along the surface of a trabecula so that a deeper cleft or "bay" appears and is filled with one or more osteoclasts, osteoblasts, connective tissue cells, and varying amounts of marrow elements. In addition, there may or may not be a blood vessel. Such changes are undoubtedly closely related to the increased intratrabecular vascularity which is so prominent in some of the cases. It is unusual to find blood vascular spaces within the trabeculae of normal vertebral bodies. In some of the cases in this series it is not uncommon to find 3 or even more vascular elements within a single trabecula included in a low power field. Such vascular spaces contain connective tissue cells, osteoblasts, osteoclasts and varying numbers of marrow elements. In most of the cases with evidence of excess destructive activity the over-all dimension of the trabeculae is not particularly reduced.

Another area where evidence of excess destruction is present is the cortex of the vertebral body. Here, intracortical vascular channels and erosions along the surface may also be found and are indistinguishable from those within and along the trabeculae of the vertebral body.

Osteomalacia: The term "osteomalacia", of course, refers to the presence of borders of non-mineral containing matrix (osteoid) along trabeculae. Such areas stain pinker with eosin than does true bone. Osteoid borders are found in appreciable amounts in 6 of the 20 cases examined but are not present in any marked excess in any of these. Examples are shown in Figures 16–19.

Osteoporosis: By "osteoporosis" one refers to bone containing a decreased number of trabeculae which in turn are thinner than normal. Four of the 20 cases of this series have this change. In order to gauge more precisely the presence or absence of osteoporosis several low power microscopic fields were projected on paper and tracings made to compare with a series of normals which has been used as a comparative group in certain other studies (3). In the cases exhibiting osteoporosis some evidence of excess destructive activity is always found. However, those cases having osteoporosis tended to have least marked evidence of osteitis fibrosa.

DISCUSSION

In 1891, F. von Recklinghausen (4) contributed his now classic monograph "Die fibröse oder deformirende Ostitis, die Osteomalacie und die osteoplastische Carcinose in ihren gegenseitigen Beziehungen" to a Festschrift in honor of Rudolf Virchow's 71st birthday. Among the 18 cases he described, one, No. XII, a 23 year old female, had exhibited clinical evidence of Basedow's disease for 5 years. A prominent feature of her illness had been pain in the back and arms. On examination kypho-scoliosis was noted. At autopsy the cortices of the long bones as well as the calvarium, scapulae and iliacs showed prominent vascular striae. All the bones sectioned like "rotten wood". Histological examination revealed spaces in the cortex containing osteoclasts. It is important to note that von Recklinghausen specifically pointed out that this young woman had never been pregnant nor had she ever evidenced manifestations of late rickets. This case was reported before the Berlin Psychiatric and Neurological Society about 6 months later by Köppen (5).

In the ensuing 60-odd years since von Recklinghausen's report (4), clinical, roentgenological, metabolic and morphologic reports have given support to the view that in certain cases of clinical hyperthyroidism skeletal lesions may be present. It is not the purpose of this discussion to detail the available literature. There are numerous clinical reports, however, of thyrotoxic individuals, usually females, who have complained of bone pain with or without spontaneous fractures of one or another bone and/or deformity of the spine (6–14). Since the first x-ray study of such a case by Kummer (9) in 1917, a number of reports dealing with roentgenological examination (predominantly of the thorax) have appeared (15–18). These have confirmed the spontaneous fractures or deformities noted clinically and have pointed out the extreme degree of rarefaction which may sometimes be present. Thus, Golden and Abbott (16) surveyed the x-rays of 110 cases of hyperthyroidism finding "slight" rarefaction in 12 and "marked" decrease in density in 3. Williams and Morgan (17) similarly surveyed roentgenograms, mainly of the thorax, from 195 cases of clinical hyperthyroidism; seven had osteoporosis of some degree.

The most convincing evidence for the importance of the thyroid gland to skeletal tissues in Graves disease has come from studies of calcium and phosphorus metabolism, particularly the excretion of these two elements. Observations by Towles (19) in 1910 on two hyperthyroid subjects indicated an increased urinary excretion of calcium. A few years later Kummer (9) noted an increased fecal excretion of this element. The first well controlled balance study was reported by the Massachusetts General Hospital group in 1929 (20). In 5 patients calcium excretion in both urine and feces was found to be markedly increased, as much as 231% above normal for a given calcium intake. Similarly there was an increased excretion of phosphorus. The effect of thyroid hormone

on calcium and phosphorus metabolism was further shown in studies on normal subjects and on a case of treated myxedema; in all, excretions of these two elements were increased. The Boston group further pointed out that neither elevated metabolic rate (20), acidosis (21) or deficiency in vitamin D (22) could explain the excessive excretion of calcium and phosphorus associated with overfunction of the thyroid gland. These metabolic balance studies have in general been confirmed by others who have used diets of varying calcium content (23–28). It has further been shown that the negative calcium balance can be restored to a positive one if larger amounts of calcium are added to the diet (29).

Metabolic studies similar to those carried out on man have been performed on animals treated with thyroid preparations. The results have in general been similar (30, 31, 32).

Autopsy studies of the skeletal tissues of patients dying in the hyperthyroid state have not been numerous since von Recklinghausen's first report in 1891 (4). Although his case No. XII of the young woman dying with Basedow's disease was called "osteomalacia", von Recklinghausen's description characterizes it more as an instance of what he chose to call "fibröse ostitis", the osteitis fibrosa of today. The important point is that von Recklinghausen indicated that bone disease may co-exist with Basedow's disease. Following the publication of his monograph several reports appeared which called attention to the occurrence of skeletal changes in Basedow's disease (8, 33). However, such reports are fragmentary insofar as any careful histological studies are concerned.

In 1930 Hunter (34) described bone changes in 2 cases of hyperthyroidism at autopsy. There was evidence of excess destruction with eroded areas filled with vascularized connective tissue and the presence of osteoclasts in Howship's lacunae.

Three years later Askanazy and Rutishauser (35) reviewed 7 autopsies on individuals dying with hyperthyroidism. In all, the typical change in the bones was osteitis fibrosa, i.e., osteoclastic resorption and increased vascularity and connective tissue proliferation. The picture corresponded to that of "progressive bone atrophy" or the "early stage of fibröse ostitis". The illustrations in Askanazy and Rutishauser's paper are similar to those we have reproduced.

Another autopsy series (12 cases) of individuals dying with Basedow's disease was reported by Martos (36). Changes indicative of excessive destruction were found in all but one.

These observations would appear to indicate without much doubt that the hyperthyroid state in addition to leading sometimes to clinical and roentgenological changes in the skeleton and disturbances in calcium and phosphorus metabolism is accompanied usually by morphological evidence of excessive bone

destruction (osteitis fibrosa). At the present time our knowledge of the intimate mechanisms of bone destruction are meager. Several factors appear to play important rôles, however: local effect of parathyroid hormone, reduction of the humoral concentrations of calcium and phosphorus, acidosis, and presence of tumor cells in the marrow cavity. The precise mechanism leading to bone destruction in hyperthyroidism is not clear. However, the excess excretion of calcium and phosphorus has been already mentioned. Most observers have not found any particular changes in serum concentrations of these two elements though Robertson's (27) studies would indicate a slight reduction in each. If, as there appears to be agreement, lime salts are lost from the organism in excess of intake, the only source can be the skeleton. After the skeletal store of mobilizable, i.e., adsorbed calcium and phosphorus is depleted, primary bone crystal and matrix must be destroyed. This, we have seen, one can demonstrate to varying degrees under the microscope. The exact cause for the excess excretion is not settled. Robertson (37) feels the mechanism is renal in origin as a result of the lowering of the renal threshold for calcium. Such an hypothesis has yet to be proved by newer clearance methods.

The presence of osteomalacic changes in some of these hyperthyroid subjects requires comment. This, of course, indicates that the humoral concentrations of calcium and/or phosphorus are not optimal to insure maximal deposition of the inorganic matrix of bone. Most observers have not found that the serum concentrations of these two elements were particularly decreased although Robertson (27), as was indicated above, has noted some reduction. The degree of osteomalacia, as we have noted, is not at all marked. Some chemical studies in the bones of hyperthyroid subjects and of animals are of interest in this regard. Osterberg and Mills (38) noted a slight average decrease (1.5–2.0%) in the ash content of bones from 20 hyperthyroid cases as compared with 78 controls. Smith and McLean (39) found no failure of calcification histologically and less than 1% difference in the ash content of thyroid treated animals. Drill (40) found a 2% decrease in the calcium content of the ash of the bones of rats fed desiccated thyroid gland. Histological studies were not carried out.

The osteoporosis which was noted in 4 of the cases of our series may be related to non specific factors such as the state of nutrition, food intake, basal metabolic rate, etc.

Correlation of the clinical data such as severity and duration of the hyperthyroid state as well as the effect of treatment, in most instances Lugol's solution, with the anatomical changes is not at all helpful. There are obviously so many variables beside degree of hyperthyroidism, such as the state of nutrition, dietary intake of calcium and phosphorus, etc., that it would appear that only controlled studies in animals can answer the many questions raised.

SUMMARY

Histological study of the vertebral bodies from 20 cases of active hyperthyroidism has been carried out. In all, evidence of excess destruction of varying degree was found. In addition, osteomalacia or osteoporosis were seen in some.

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PLATE I

FIG. 1. (8233). Trabecula showing irregularly eroded surface on one side giving it a local "saw tooth" appearance.

FIG. 2. (8233). Trabecula showing erosion with filling of eroded portion by marrow cells. Note long thin spicule of bone projecting from left.

FIG. 3. (11483). Trabecula showing two local areas of destruction (arrows).

FIG. 4. (11483). Trabecula showing 3 intratrabecular foci of marrow replacement. Such foci are not seen in normal bones.

FIG. 5. (12880). Trabecula showing irregularities along both upper and lower surfaces.

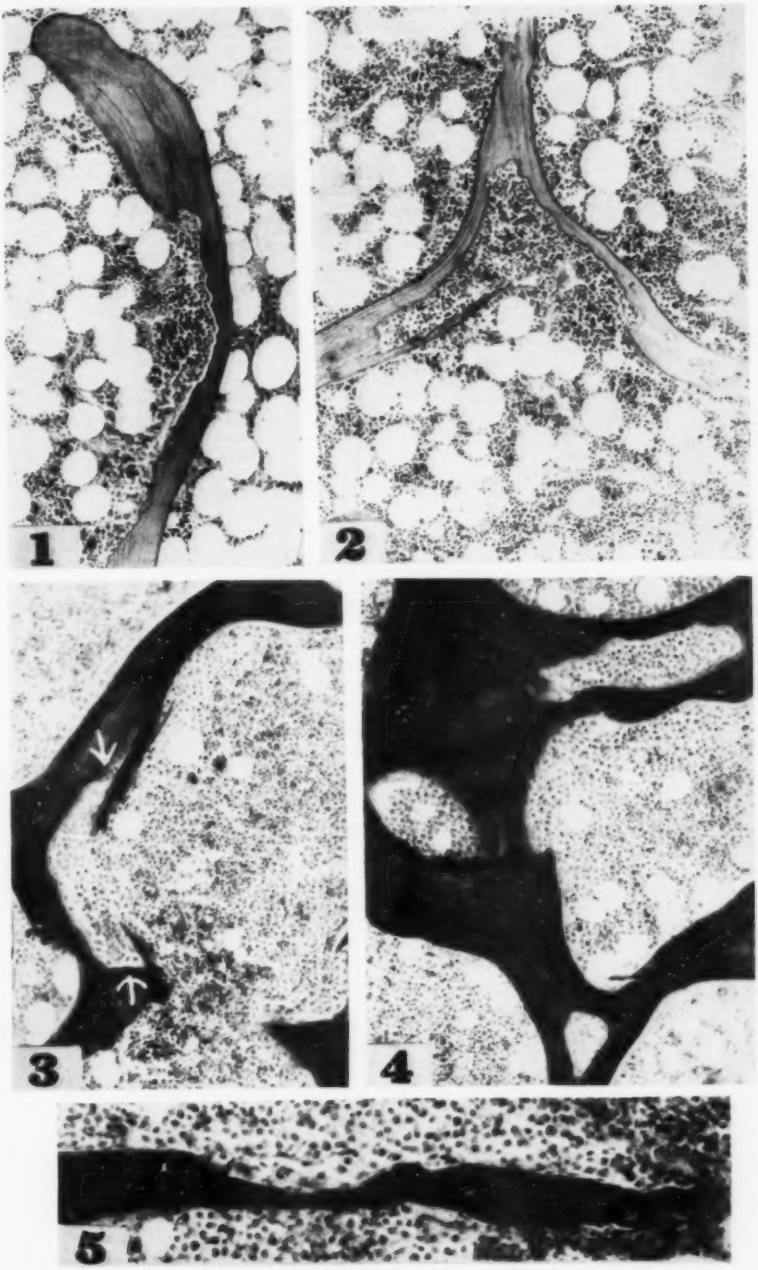
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PLATE II

FIG. 6. (17498). Two trabeculae each with localized eroded areas.

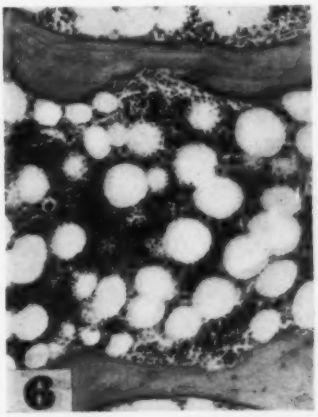
FIG. 7. (12318). Trabeculae with large eroded focus which extends deep at bottom of picture (arrow).

FIG. 8. (12976). Two trabeculae, each with prominent eroded foci.

FIG. 9. (12851). Trabecula with intratrabecular focus of osteitis fibrosa containing blood vessel and a giant cell.

FIG. 10. (12318). Focus in cortex of vertebra showing several giant cells and scalloped margins.

FIG. 11. (16324). Two foci in cortex of vertebra showing aggregation of osteoclasts.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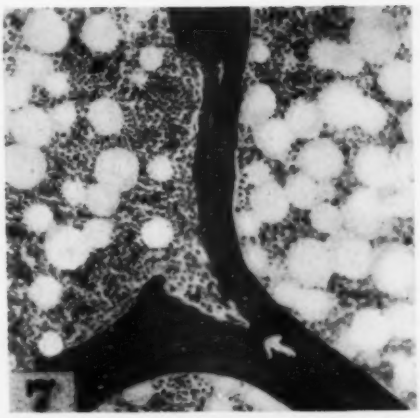
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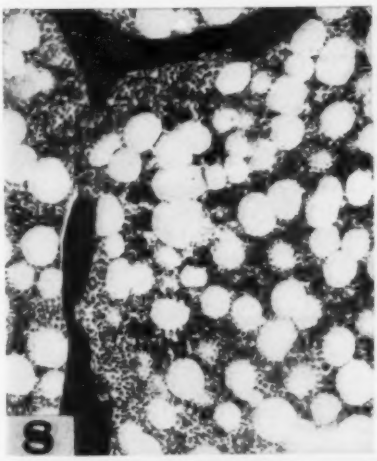
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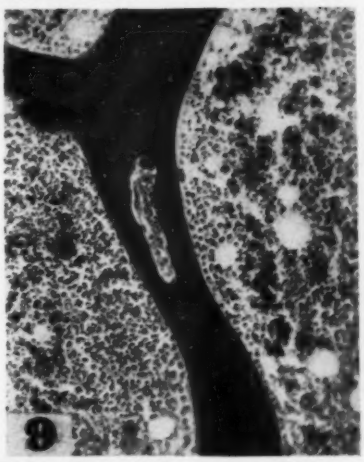
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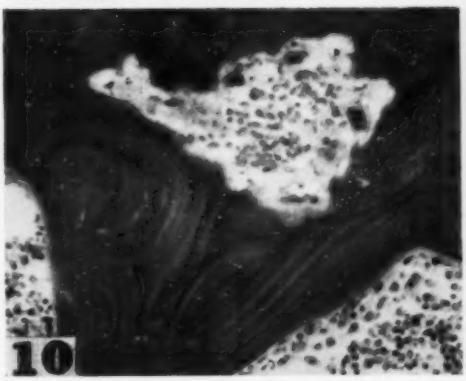
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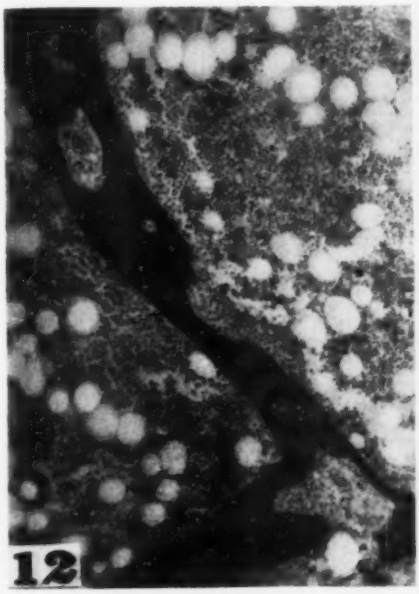
PLATE III

FIG. 12. (13812). Several intratrabecular and peritrabecular foci of erosion (See Figure 23).

FIG. 13. (13821). Higher power of an intratrabecular focus of erosion with 2 osteoclasts, connective tissue cells, marrow elements and blood vessels.

FIG. 14. (18510). Intratrabecular defects. Note prominent osteoblasts about margins.

FIG. 15. (18510). Two intratrabecular foci containing blood vessels, connective tissue cells and osteoblasts.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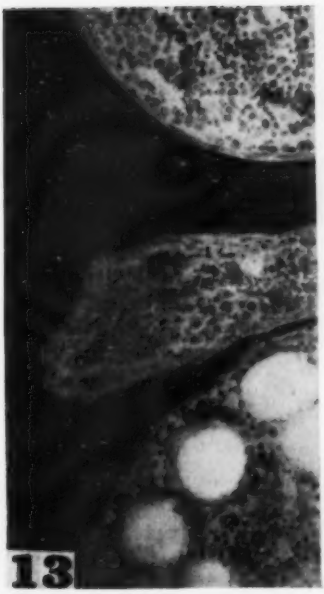
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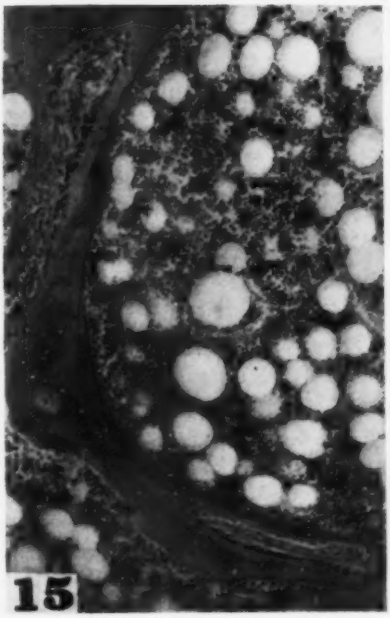
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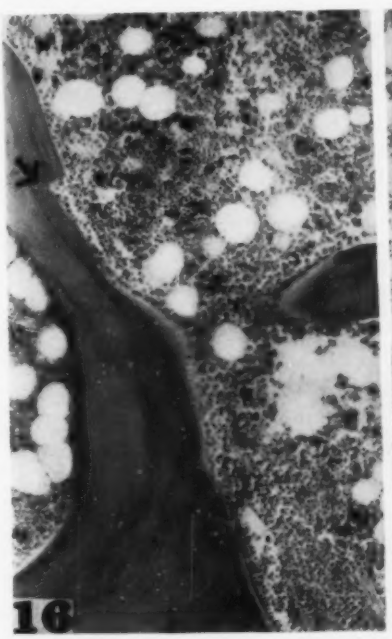
PLATE IV

FIG. 16. (13226). Osteoid borders (light staining zones) along 2 trabeculae. In addition there is a small eroded focus at arrow.

FIG. 17. (11175). Osteoid borders along a branching trabecula.

FIG. 18. (13226). Osteoid border along trabecula. Note non-uniformity of distribution.

FIG. 19. (15011). Osteoid borders along trabecula.



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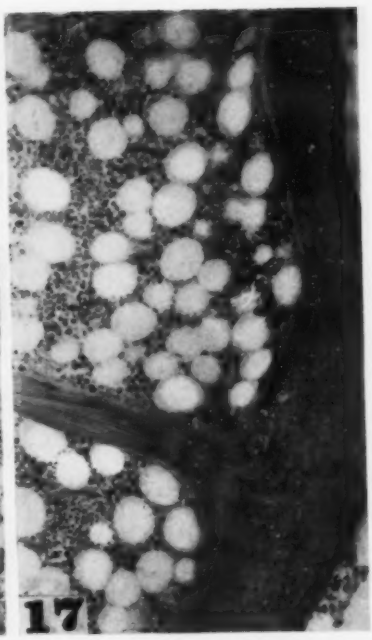

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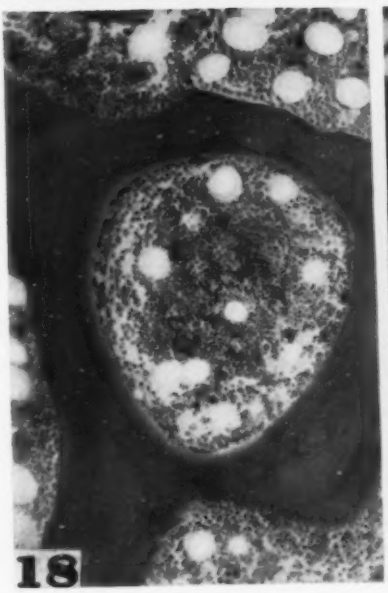

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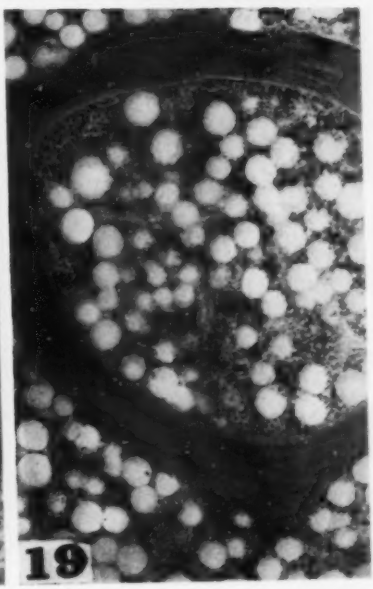

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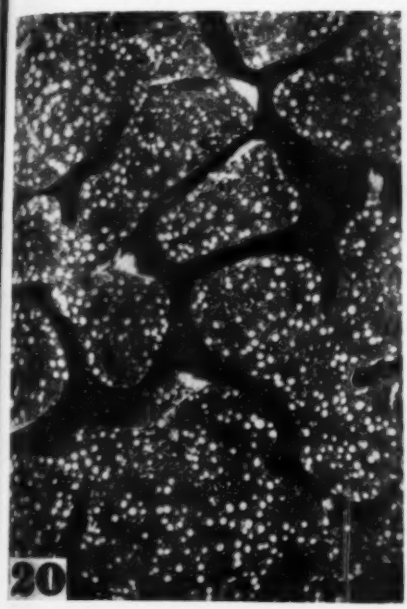
PLATE V

FIG. 20. (16746). Low power of normal vertebral body to show number and size of trabeculae.

FIG. 21. (11175). Great decrease in number and size of trabeculae as compared with normal (Fig. 20).

FIG. 22. (12976). Decrease in number and size of trabeculae.

FIG. 23. (13821). Trabeculae are normal in number and size. Note intratrabecular defects. (See Figs. 12 and 13.)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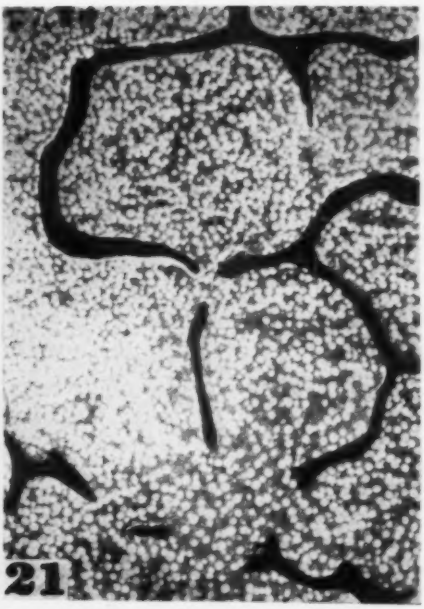
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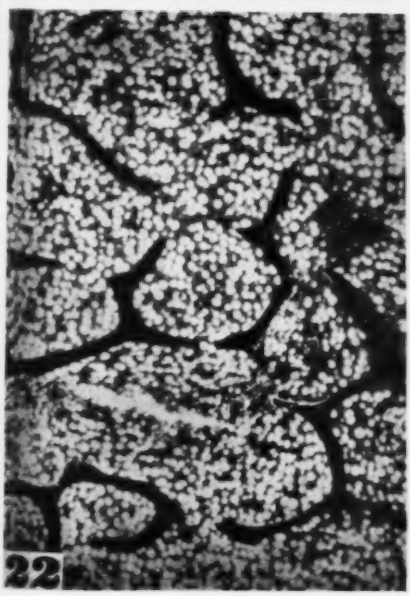
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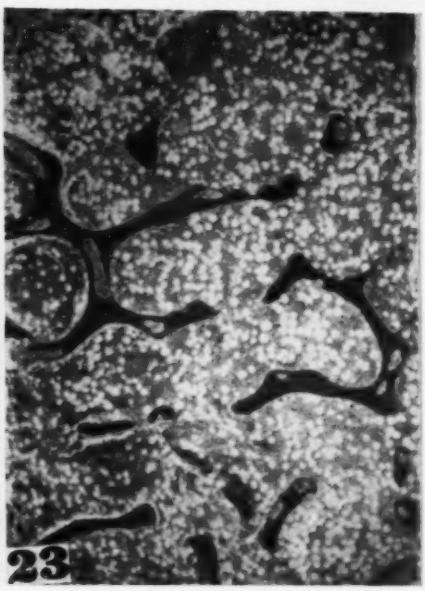
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A NOTE ON PERIPHERAL BLOOD VASCULAR BEDS IN THE BULBAR CONJUNCTIVA OF MAN

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An earlier report from this laboratory (1) included a group of observations upon peripheral blood vascular beds in the bulbar conjunctiva of man. The observations indicated that the vascular patterns "may exhibit endless variety, at times to the point of apparent 'randomness', and suggesting no definite plan of organization interpretable in terms of structural units of the most ill-defined sort." On the other hand, Chambers and Zweifach (2)—on the basis of extensive studies of the frog's mesentery, the rat's mesoappendix and the dog's omentum—had arrived at a concept of the peripheral vascular bed as a composite of structural and functional units, each unit having as its basic architectural feature a central, capillary-like, arterio-venous, preferential or "thoroughfare" channel, of which the true capillaries are side-branches. Lee and Holze (3, 4) interpreted their findings in terms of the full applicability of this concept to the human bulbar conjunctiva. As noted elsewhere (1), "The area of disagreement is wide, and there is an obvious need for further detailed studies in this region." An acute awareness of this need has led us to re-investigate the problem, with markedly improved equipment, in an attempt to resolve apparent discrepancies in the findings of the two groups of investigators.

For our current studies, of which this is a preliminary report, we have employed a Zeiss Opton Stereo-Microscope, provided with 2× supplemental lens, in a range of from 6 to 80 magnifications; and a Mikrark (wolfram-zirconium) Illuminator with 100 watt bulb (Boone Instrument Co., New York), and provided with heat-absorbing and Wratten green (Eastman B, no. 58) filters. Subjects have been studied in the recumbent position, using angular incident illumination. Under these conditions, we have been able to achieve far better visualization of certain features of the conjunctival vascular beds than in previous studies (1), which were clearly inadequate in a number of important respects.

Our recent experience confirms the endless variety of the vascular patterns, and the lack of any recognizable structural and functional unit in the sense of Chambers and Zweifach. However, interposed between obviously arterial and obviously venous channels, we have repeatedly encountered—in addition to presumptive "true capillaries"—vessels of appreciably larger than capillary size, and apparently of the nature of arterio-venous communications, of

quite different functional significance than the capillaries themselves. Though variable in speed, the flow in these vessels is continuous at all times, even when the presumptive "true capillaries" are intermittent or inactive. These arterio-venous communications are of such frequent occurrence as to constitute a characteristic feature of the peripheral vascular beds; and would appear to be equivalent to at least some of the "A-V thoroughfares" and "through and through channels" of Lee and Holze (3, 4) and of Lack *et al.* (5), respectively. Their more exact characterization must await further study.

Variably active "vasomotion"—in the sense of variations in speed of flow, alterations in caliber of individual vessels, and irregular alternation between activity and inactivity (i.e., intermittence) of capillaries—can be detected regularly and with ease. Visualization of flow in obviously arterial channels, including the smallest ones, presents no appreciable difficulty. The more usual picture is one of essentially continuous flow at good speed, sufficiently rapid so that individual erythrocytes cannot be recognized. However, the pictures can vary over a considerable range. At times, the flow alternates irregularly between more and less rapid rates, but remains continuous. At other times, a rapid flow is reduced more or less gradually or abruptly, and comes almost to a halt (or on occasion stops altogether) for a brief interval; then surges forward again, rather quickly attaining a variably rapid rate. This type of irregularly surging flow may be continued over appreciable periods and is rather striking. On occasion, with a forward surge of blood, the smaller arterial channels appear definitely to increase appreciably in caliber. While frequently exhibiting surging flow and variations in diameter during active "vasomotion" of the parent artery(ies), it is often difficult to decide whether the arterio-venous communications (as described above) are showing active or only passive caliber changes.

As additional findings, we have encountered arterio-venous anastomoses of rather large caliber, as well as unmistakable arterio-arterial and veno-venous anastomoses of considerable size. In the latter two types of vessel, reversal in the direction of blood flow is not infrequently observed.

SUMMARY

As a supplement to earlier studies, a description is given of various aspects of peripheral blood vascular beds in the bulbar conjunctiva of man. These include arterio-venous communications, of such frequent occurrence as to constitute a characteristic feature; "vasomotion"; and arterio-arterial, arterio-venous and veno-venous anastomoses.

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THE RELATIONSHIP OF VITAMIN D ADMINISTRATION TO THE PREVALENCE OF RICKETS OBSERVED AT AUTOPSY DURING THE FIRST TWO YEARS OF LIFE*

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In a preceding paper (1) data have been presented which deal with the prevalence of rickets in a series of 1303 subjects coming to autopsy during the first two years of age. A high incidence of rickets of moderate or severe degree was found in these children, particularly those observed after the first two months of age. Rachitic changes were more prominent in the negro children. Prematurity appeared to have relatively little influence on the over-all prevalence or severity of the disease. In this communication we should like to present data which deal with the relationship of vitamin D intake to the prevalence and severity of bone lesions in the same series of 1303 children.

VITAMIN D ADMINISTRATION

In any discussion dealing with an assessment of vitamin intake certain fundamental points must be made clear. In the first place one is wholly dependent on those data furnished by the clinical history. As has been pointed out elsewhere (2) in a discussion of the validity of vitamin C administration in this same group of 1303 children, we have been severely handicapped by the unreliability of the histories. This results from a variety of factors: the unintelligence and dishonesty of certain mothers; a lack of knowledge of the individual, possibly a neighbor or sibling, who brought the child to the hospital; or the failure of the doctor taking the history to obtain pertinent data. We are left, therefore, with only a relatively small group of subjects who are deemed suitable for analysis. These children have been carefully screened and may be divided into two groups: (1) those patients in whose record there is a definite statement that *no* form of vitamin D had ever been administered either at home or in the hospital and (2) those to which *known* amounts of vitamin D had been administered for varying periods in the hospital prior to death.

DEFINITE HISTORY OF NO VITAMIN D ADMINISTRATION IN FULL TERM GROUP

There were 147 full term children, one through 24 months of age, who had a definite history of never having received vitamin D throughout their entire

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life. Data dealing with these children are presented in Table I. Rickets was present in 102 infants or 69% of the total. The disease was classified as moderate or severe in 74 (72%) of the 102 children in whom the diagnosis was made.

Therefore, roughly half of this series of 147 full term children to whom vitamin D had never been administered show moderately or severely advanced rickets, while the remaining half show either no or slight evidence of the disease. The findings in the first group are, of course, as one would have expected. On the other hand, why did rickets not develop at all or to only a slight degree in the others?

TABLE I

Full Term Children in Whom There Was a Definite History of No Vitamin D Administration

AGE IN MONTHS	TOTAL CASES	NUMBER WITH RICKETS	NUMBER WITH MODERATE OR SEVERE RICKETS
1	18	12	9
2	12	11	7
3	13	12	9
4	19	13	9
5	15	12	8
6	11	6	6
7–12	36	24	16
13–24	23	12	10
Totals	147	102	74

To cast further light on this problem we have analyzed these 147 cases with respect to: (1) nutritional status at the time of death, (2) duration and severity of the disease leading to death, and (3) month of year at time of death.

Information concerning the state of nutrition at the time of death has been obtained from the clinical records and autopsy protocols. The child in question has been described as "emaciated" as of a "poor", "fair" or "good" state of nutrition. The results of this analysis are shown in Table II where it will be noted that there were about equal numbers of children in the emaciated—poorly nourished group with or without moderate or severe rickets as there were in the fair or good status of nutrition group. Thus the development of rickets would not appear to be influenced by the state of nutrition.

These 147 children have been separated into 3 groups as to the duration of their terminal illness: acute (1–14 days); subacute (15–28 days), and chronic (over 28 days). There was no relationship between the duration of terminal illness and the presence or absence of moderate or severe rickets.

When the group having no or slight rickets was compared with that having moderate or severe skeletal involvement from the standpoint of month of

year at time of death, no greater numbers were found in the winter than in the summer months. Variations in response to sunlight would therefore not appear to explain the lack of development of moderate or severe rickets in half of these children never having received vitamin D.

Is there any other explanation? In certain instances, but in by no means all, the answer is "yes". We base this on the observation that in some cases growth of the cartilage cells appears either to have slowed considerably or to have stopped altogether. Growth, of course, is necessary for rickets to manifest itself. Evidence of "growth suppression" was seen in 24, or one-third of the 73 cases having no evidence of or only a slight degree of rickets (Figures 5 and 8). The cause for the non-development of moderate to severe skeletal disease in the remainder is not clear.

TABLE II

Relation of Nutritional Status to Presence of Rickets

NUTRITIONAL STATUS	NUMBER CASES WITH NO OR SLIGHT RICKETS	NUMBER CASES WITH MODERATE OR SEVERE RICKETS
Emaciated—Poor	19	23
Fair—Good	46	44

It is of interest to examine the lesions encountered in the earlier months, i.e., the first and second, in order to point out the degree of rickets which may be manifested in so short a period. We have indicated elsewhere (1) that we have encountered only two instances of rickets during the first two weeks of life. After this time the disease becomes much more prevalent. In the age period 16 to 30 days rickets was present in 61.2% of 90 subjects examined and was classed as of moderate or severe degree in two-thirds of these (1). It is clear, therefore, that only a relatively short time is needed to elapse before rachitic changes may appear at the growing ends of the bones (Figures 1–4). On the other hand certain children may grow in normal fashion in the absence of vitamin D and show no evidence of rickets at autopsy (Figures 6 and 7).

DEFINITE HISTORY OF NO VITAMIN D ADMINISTRATION IN PREMATURE GROUP

In the first through the 6th month period there were 119 premature infants available for study. A definite history of no vitamin D administration was present in 16 of these. There is no point in tabulating such a small group; it is sufficient to say that 12 of these infants had evidence of rickets which was of moderate or severe degree in 8 (Figures 9–11). Of the 88 full term children, aged 1 through 6 months of age receiving no vitamin D, 48 (54%) had moderate or severe lesions. There is thus no difference in the severity of skeletal changes in the premature (50%) as compared with the full term group.

DEFINITE HISTORY OF DAILY VITAMIN D ADMINISTRATION IN FULL TERM GROUP

There were 107 full term children in whom there was a definite statement in the history that vitamin D had been prescribed during the time the individual was in the hospital. In a previous communication (1) we have commented on the difficulties in estimating the duration and severity of rachitic changes from an examination of the skeletal tissues at autopsy. Here we are faced with a somewhat similar and more complex problem which has even more variables: the amount and duration of known vitamin D administration in the hospital as well as in some an unknown ingestion before hospitalization; factors dealing with the absorption of vitamin D; exposure to sunlight; disturbances in calcium and/or phosphorus metabolism and absorption as a result of illness, particularly diarrhea; rate of growth of skeleton; and the type and duration of the terminal illness.

TABLE III

Relationship Between Daily Amounts of and Duration of Vitamin D Administration in No or Slight and Moderate or Severe Rickets Groups

UNITS VITAMIN D ADMINISTERED	NO OR SLIGHT RICKETS DURATION ADMINISTERED (DAYS)		MODERATE OR SEVERE RICKETS DURATION ADMINISTERED (DAYS)	
	7–20	21 and over	7–20	21 and over
0–1000	3	10	6	7
1000–2000	2	9	7	5
2000–3000	3	7	4	6
3000 on	3	14	14	7
Total	11	40	31	25

The findings for this group are summarized in Table III, where it will be noted the subjects have been divided into 2 groups: those having evidence of no or slight rickets and those having moderate or severe skeletal involvement. Vitamin D administration has been tabulated as to dosage and duration of therapy. We have arbitrarily divided the latter into 2 periods, 7 to 20 days and 21 days or over. This broad grouping is to be preferred because of the small number of cases available for study. Even so, conclusions are difficult to draw. Although there appear to be more cases in the no or slight rickets group treated for more than 3 weeks, an appreciable number is still found in the moderate or severe group. These 13 bear further analysis and are summarized in Table IV where those receiving 2000 units daily of vitamin D or more for over 21 days are tabulated. Three (1623, 1689, 1364) have reason for poor vitamin D absorption as a result of biliary, or pancreatic duct obstruction. Healing is present in 6. The reason for rickets with no evidence of healing in the remaining 4 is not clear.

This entire group of treated children is of great interest since evidence of

healing was found in some to whom known amounts of vitamin D had been administered for varying periods. Histological indication of healing (Müller's sign) was observed earliest in an 8 month old infant receiving 13200 units of vitamin D daily for only 13 days (Figures 14 and 15). This effect could not be detected in the post-mortem roentgenograms of the ribs. From this time on up to and past 3 weeks of age evidence of healing was observed in a num-

TABLE IV

Summary of 13 Full Term Children With Moderate and Severe Rickets With 2000 or More Units of Vitamin D for 21 Days or Over

NUMBER, AGE IN MONTHS	DAILY UNITS VIT. D RECEIVED, DAYS BEFORE DEATH	DURATION AND SEVERITY OF TERMINAL ILLNESS	DURATION AND SEVERITY OF RICKETS, WITH OR WITHOUT HEALING
1055, 2 mo.	2220, 40 d.	Cong. syphilis; erysipelas	Subacute, moderate, healing
1553, 2 mo.	3330, 22 d.	Chr. meningitis, 5 weeks	Subacute, moderate, no healing
1623, 6 mo.	2220, 90 d.	Cong. obst. bile duct	Chronic, moderate, no healing
1689, 7 mo.	2220, all life	Cystic fibrosis, pancreas	Subacute, moderate, no healing
951, 8 mo.	2220, 27 d.	Cong.malform. brain; sepsis	Subacute, moderate, healing
1364, 10 mo.	4440, 63 d. 13200, 14 d.	Cystic fibrosis, pancreas	Subacute, moderate, no healing
1726, 10 mo.	3330, 111 d.	Subdural hematoma	Chronic, moderate, no healing
489, 11 mo.	13200, 21 d.	Chronic tuberculosis	Subacute, severe, healing
1198, 12 mo.	4440, 25 d.	Pneumococcal pneumonia and meningitis	Acute, moderate, no healing
1452, 12 mo.	2220, 24 d.	Healing burns; healed scurvy; sepsis, and meningitis	Chronic, moderate, healing
813, 13 mo.	8880, 70 d.	Chronic tuberculosis	Chronic, severe, healing
1208, 15 mo.	2000, 30 d.	Chronic dysentery	Subacute, moderate, no healing
1105, 18 mo.	2220, 37 d.	Empyema, erysipelas, 6 weeks	Subacute, moderate, healing

ber of children receiving varying amounts of vitamin D as illustrated in Figures 12–18.

DEFINITE HISTORY OF DAILY VITAMIN D ADMINISTRATION IN PREMATURE GROUP

There were 30 prematures up to 6 months in age in whom it was stated in the history that vitamin D had been administered for varying periods before death. Twenty-two of these evidenced moderate or severe rickets while 8 showed no or slight skeletal involvement.

In Table V are shown data dealing with the rachitic group. Different amounts of vitamin D were administered for varying times. An overall precise summary

TABLE V

Selected Prematures Showing Moderate or Severe Rickets Who Had Received Vitamin D before Death

NUMBER; AGE IN DAYS; BIRTH WT. IN GMS.	DAILY UNITS VITAMIN D RECEIVED, DAYS BEFORE DEATH	DURATION AND SEVERITY OF TERMINAL ILLNESS	DURATION AND SEVERITY OF RICKETS
910, 32 d. 1650 gm.	2220, 28 d.	Acute sepsis	Acute, moderate
779, 33 d. 1600 gm.	4440, 7 d. 6660, 16 d.	Chronic malnutrition with terminal A.N.D.	Subacute, moderate
1189, 33 d. 1900 gm.	4440, 19 d. 0, 9 d.	Staphylococcus sepsis, acute	Acute, severe
1554, 34 d. 1200 gm.	3330, 5 d. 6660, 16 d.	Acute pneumonia	Subacute, moderate
1705, 34 d. 1900 gm.	6660, 25 d.	Aspiration pneumonia	Subacute, moderate
1652, 37 d. 1025 gm.	6660, 30 d.	Acute, unexplained	Subacute, moderate
13, 42 d. 1500 gm.	400, 15 d. 800, 6 d.	Acute respiratory infection	Subacute, moderate
1428, 46 d. 2150 gm.	2220, 37 d.	Acute nutritional disturbance	Subacute, severe
897, 69 d. 1900 gm.	6660, 23 d.	Acute nutritional disturbance	Subacute, severe (figure 23)
1436, 71 d. 1500 gm.	3330, 71 d.	Congenital tuberculosis	Subacute, severe
744, 72 d. 2100 gm.	4440, 30 d. 0, 5 d.	Acute nutritional disturbance	Subacute, severe
1003, 73 d. 2000 gm.	2220, 6 d. 3330, 57 d.	Acute enteritis	Subacute, moderate
958, 78 d. 1600 gm.	2220, 18 d. 3330, 25 d. 4440, 18 d.	Acute sepsis	Subacute, severe
1417, 84 d. 1400 gm.	4440, 6 d. 6660, 47 d. 4440, 6 d.	Acute nutritional disturbance	Subacute, severe
1572, 87 d. 1000 gm.	660, 17 d. 1110, 26 d. 4440, 30 d.	Sudden death, transfusion	Subacute, moderate
1205, 109 d. 1300 gm.	3330, 49 d. 4440, 87 d.	Acute pneumonia, renal tubular disease?	Chronic, severe
1081, 114 d. 1400 gm.	3330, 110 d.	Acute sepsis	Subacute, moderate (figure 22)
802, 115 d. 2000 gm.	3330, 87 d. 5550, 13 d.	Acute pneumonia	Subacute, moderate
1418, 132 d. 1020 gm.	3330, 19 d. 6660, 64 d.	Subacute nutritional disturbance	Subacute, moderate
1348, 159 d. 1600 gm.	3330, 146 d.	Chronic empyema	Chronic, moderate (figure 21)
1511, 174 d. 2000 gm.	3330, 32 d.	Chronic enteritis	Acute, severe (figure 20)

cannot be made. However, if all these cases are examined it will be noted that large doses, up to 6660 units daily for at least a month before death failed to protect. Evidence for healing was difficult to evaluate but was seen in several. The degrees of rickets found in the bones of these children in the face of treatment are exemplified in Figures 20–23.

DISCUSSION

In this series of 1303 children who were studied at autopsy it is unfortunate that in so few were data available to afford a correlation of the morphological changes with vitamin D administration during life. We are left with only a small number, 300 in all, which may be divided into 2 categories: those to whom no vitamin D had ever been administered and those who had received it before death in varying amounts for different periods of time while in the hospital. It seems worthwhile to present the data which have been accumulated since they are unique and can probably never be gathered together again because of the great change in the pattern of disease in pediatric practice as result of chemotherapy.

As one might have expected, a large proportion of both full term and premature children to whom vitamin D had never been administered either at home or while in the hospital showed rickets. However, even in those evidencing rachitic changes there was a great deal of variation which may in part be related to the mineral stores at birth, amount and kind of milk consumed, rate of growth, general nutritional status, type and duration of terminal illness and season of the year. We are unable to determine the status of mineral stores at birth nor were data available as to the precise type of milk used. In some, irradiated canned milk was doubtless used. It has been noted above that nutritional status, duration of terminal illness and month of year did not seem to play any particularly important role. One is, therefore, faced with the possibility, which as data accumulate becomes a probability, that the vitamin D requirement of each individual may be the most important variable. The cases which we have presented taken together with those of "vitamin D resistant rickets" now accumulated in the literature certainly suggest that individual requirements for vitamin D must be most diverse. It is quite possible that there are some humans who approach the rat in needing virtually no exogenous vitamin D to protect against rickets, providing dietary calcium and phosphorus are adequate, while others need a great deal more than the "normal". Whether variation in vitamin D requirement is the whole story obviously requires further study, since individual variation in calcium requirement, at least in adults, would also appear to be diverse (3).

Studies on normal infants from birth through several months thereafter have not been carried out with respect to calcium and phosphorus balance

and the effect of the addition of vitamin D. Such data are certainly needed and might help clarify our own observations.

When the full term and premature children who received known amounts of vitamin D are examined, more difficulties arise. We have already cited some of the variables, whose importance is so difficult to assess, which operate in the full term group. Because of these it is to be regretted, though hardly unexpected, that our data do not allow any definite conclusion as to the levels of vitamin D administration which will insure the absence of rachitic changes in the skeleton of the full term child. The data do indicate, however, that in an *hospital population*, i.e., one composed of sick children, (and we wish to stress that this is a specialized group), daily amounts of 400–800 units of vitamin D would not always appear to protect full term infants under one year of age. Because of the reasons already cited we did not feel safe in trusting the history of vitamin D administration when the child was not on the wards. Hence, no data are available with which to correlate morphologic changes and over-all vitamin intake in children acutely ill for only a short period before death. Such individuals would conform more closely to the population as a whole. It is likely that we shall never know the exact prophylactic dose of vitamin D in the average well child.

One of the most interesting parts of this study has been the analysis of the premature group, aged 1 through 6 months of age, who received known quantities of vitamin D. Even though seemingly adequate amounts of the vitamin were administered to many, rickets of a moderate or severe degree was present in a high proportion of cases. It is not necessary to go into the various physiological deficiencies which beset the premature infant at birth, difficulties which in contrast the full term infant does not have to face. Absorption and storage of calcium and/or phosphorus, absorption of vitamin D, excessively rapid growth of the skeleton, predisposition to infection, all are important. The cases we have cited in the premature group serve to exemplify how rickets may develop even when relatively large amounts of vitamin D are administered.

The question, of course, arises: is rickets "normally" present in the rapidly growing premature ingesting a maximal quantity of milk and as much as 6000 units vitamin D each day? Such a concept would mean that cartilage and bone matrix production outstrips the ability of inorganic salts to be deposited in it. Such in truth may be the case. One encounters distinct bands of osteoid along the trabeculae in the rapidly growing infant, borders which we and others have called "physiological osteoid". So too, the quantity of inorganic materials in the zone of provisional calcification of the cartilage varies so that one can only pick an arbitrary "normal" based on one's own experience. At any rate it is quite obvious that histological observations

such as those which we have presented furnish the most precise information of the relationship of vitamin D administration to the development of rickets in the premature infant and are more exact than roentgenological or chemical examinations, upon which vitamin requirements in the past have been based.

Morphological changes indicative of healing in rickets have been recognized for almost 100 years since Müller first described the healing line of lime salt deposition which bears his name (4). The clinician has noted this phenomenon in x-ray films; the pathologist has not often had the opportunity to examine such material at autopsy. The descriptions and published illustrations of Schmorl (5) are the exception. Schmorl's study is of interest to compare with the present report and our previous one (1). The rickets which he studied in Dresden during the years 1901 to 1908 was uncomplicated by many of the factors which tend to make our study so complex. Dresden is farther north than Baltimore; hence, the influence of sunlight is less. The population in Dresden was more homogenous than our mixture of white and negro children. There was more uniformity in feeding, i.e., breast rather than cows or canned milk. Prophylaxis or therapy with vitamin D was unknown to Schmorl.

The histological preparations we have presented in Figures 12 to 18 are unique in that some correlation may be drawn between presence and degree of healing and amount and length of time of vitamin D administration. The latter data are provided in the legends for the figures. We shall present a detailed resumé of our observations on healing rickets elsewhere (6).

SUMMARY

The prevalence of rickets at autopsy in 300 children between the ages of one and twenty-four months has been correlated with the known non-administration or administration of vitamin D.

One-half of the children never having received vitamin D showed moderate or severe rickets. Factors affecting the non-development of rickets in the remainder are discussed.

Among children, both full term and premature, who received known amounts of vitamin D for varying periods before death, there was great variation in the severity of rickets found at autopsy. The complex nature of the variables, of which vitamin D is only one, which affect the development of rickets, is discussed.

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6. Follis, R. H., Jr. and Park, E. A., To be published.

EXPLANATION OF FIGURES

PLATE I

FIG. 1 (80). Costochondral junction from a 42 day old full term well nourished infant dying of pneumococcal meningitis of 9 days duration. Never had received vitamin D. Note defective calcification of cartilage. Rickets, acute moderate.

FIG. 2 (953). Costochondral junction from a 61 day old full term well nourished infant dying of a congenital malformation of the heart. Never had received vitamin D. Rickets, acute moderate.

FIG. 3 (1363). Costochondral junction from a 2 months old full term well nourished infant dying of tuberculosis. Never had received vitamin D. Rickets, subacute severe.

FIG. 4 (1397). Costochandral junction from an extremely emaciated full term child dying of enteritis. Had never received vitamin D. Rickets, subacute severe in presence of severe malnutrition.

FIG. 5 (1212). Costochondral junction from a 6 months old full term fairly well nourished child dying of dysentery of 2 weeks duration. Never had received vitamin D. There is inhibition of growth of cartilage. No rickets present.

FIG. 6 (1154). Costochondral junction from a 7 month old full term well nourished infant dying of meningitis of 2 weeks duration. There is no suppression of growth of cartilage. There is a prominent lattice of calcified cartilaginous matrix. Never had received vitamin D. No rickets present.

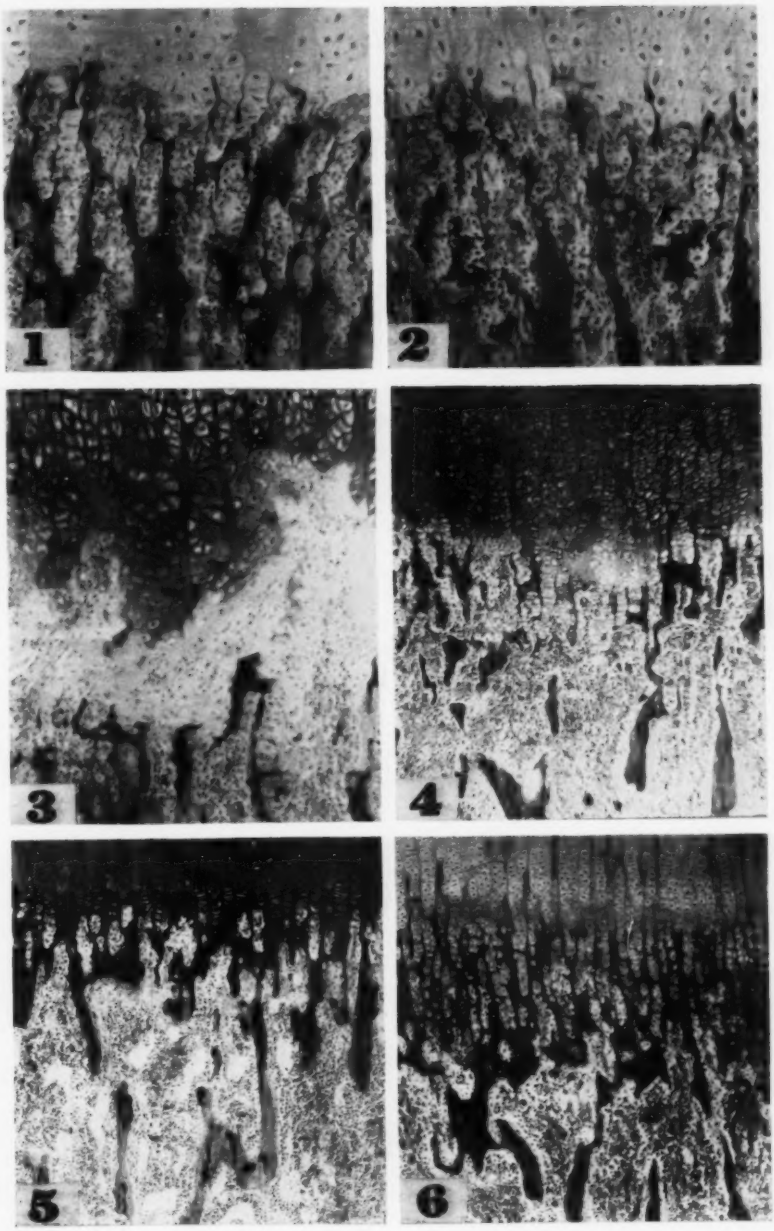
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Plate II

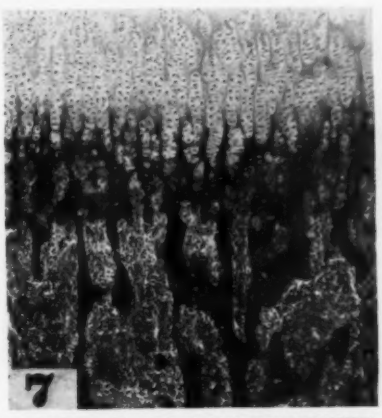
Fig. 7 (1172). Costochondral junction from a 10 month old full term well nourished infant dying of pneumonia and pericarditis of 12 days duration. Growth activity of the cartilage is not impaired. Had never received vitamin D. No rickets present.

Fig. 8 (1322). Costochondral junction from a 4 month old full term poorly nourished child dying of acute nutritional disturbance of 16 days duration. There is inhibition in growth of the cartilage. No vitamin D had ever been given. No rickets present.

Fig. 9 (32). Costochondral junction from a 57 day old premature weighing 1690 grams at birth. Nutrition was poor; death resulted from pneumonia of 12 days duration. Vitamin D had never been administered. Rickets, acute moderate.

Fig. 10 (210). Costochondral junction from an 86 day old premature dying of sepsis, duration unknown. Nutrition was poor. Had never received vitamin D. Rickets, subacute moderate.

Fig. 11 (136). Costochondral junction from a 93 day old premature weighing 2300 grams at birth. Child died of pneumonia following pertussis and was emaciated. No vitamin D had ever been administered. Rickets, chronic severe.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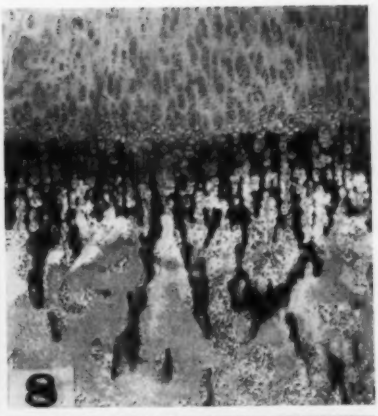
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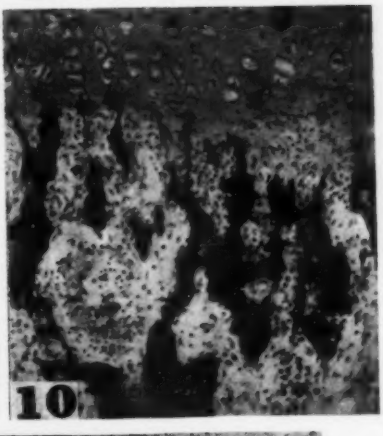
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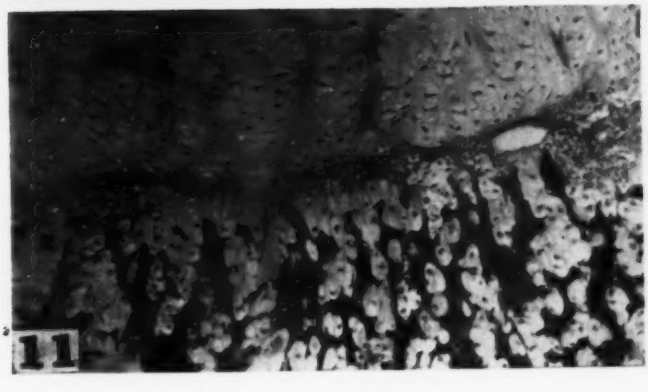
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Plate III

Fig. 12 (506). Costochondral junction from a 10 month old full term well nourished child dying of pneumonia after an illness of 16 days. No vitamin D until hospital, then 1000 units for 14 days. Healing line present.

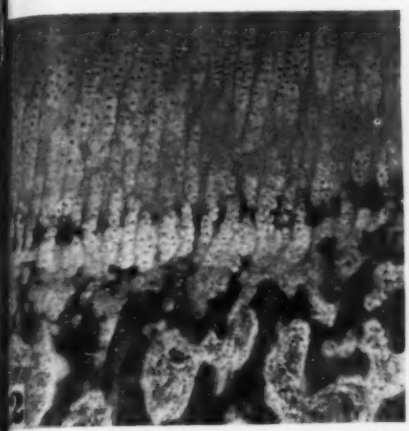
Fig. 13 (951). Costochondral junction from an 8 month old full term well nourished child dying of pneumonia and sepsis, 30 days duration. No vitamin D except 2220 units for last 30 days in hospital. Healing line present.

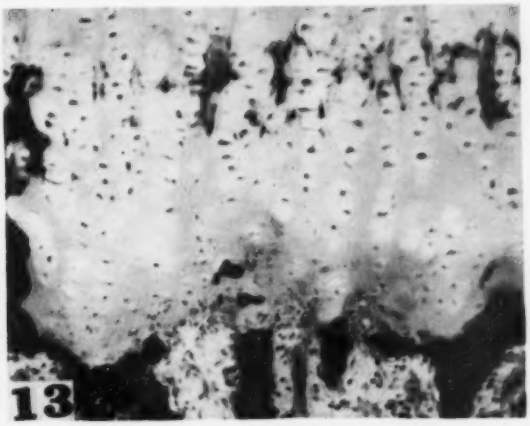
Fig. 14 (203). Cartilage shaft junction of upper end of femur from an 8 month old full term, fairly well nourished child dying of tuberculous meningitis. No vitamin D received except 13200 units daily for last 13 days. Healing line present.

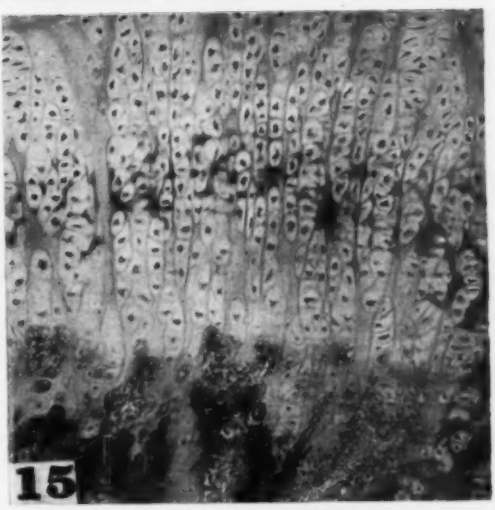
Fig. 15 (203). Higher power of area marked in Figure 14.

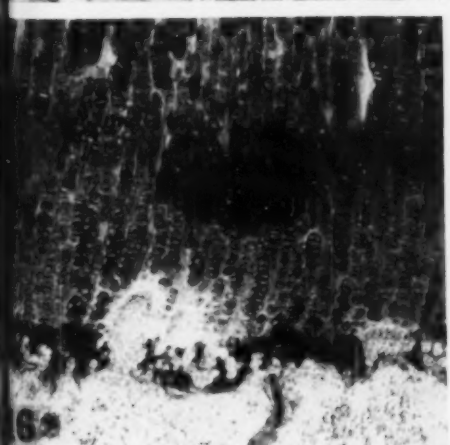
Fig. 16 (489). Costochondral junction from an 11 month old full term child who was poorly nourished and died of chronic tuberculosis. Vitamin D, 13200 units, administered daily for 21 days. Rickets, subacute severe with healing.

Fig. 17 (550). Costochondral junction from 3 month old full term child dying of pneumonia of 3 weeks duration. Vitamin D, 4440 units had been administered daily for 14 days. Rickets, subacute severe with healing.









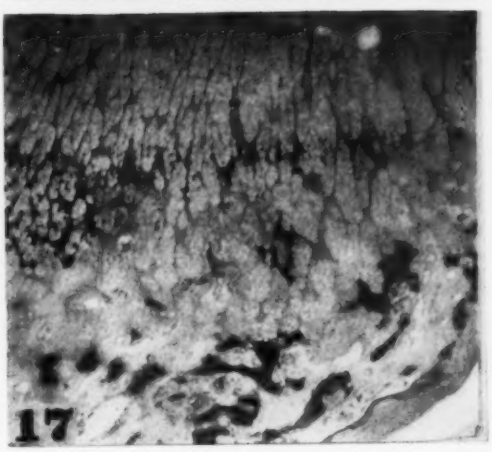


PLATE IV

FIG. 18 (211). Costochondral junction from a 6 month old full term infant who was poorly nourished and failed to gain all its life. Death occurred from sepsis. Vitamin D, 400 units daily, all its life. Rickets, chronic severe with healing.

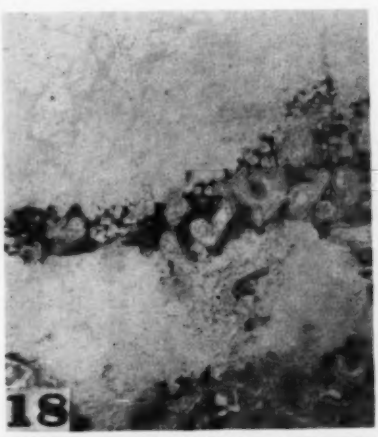
FIG. 19 (838). Costochondral junction from a 2 month old full term well nourished infant dying of dysentery of 19 days duration. Had received vitamin D, 2220 units daily for 10 days. Rickets, subacute severe; no healing.

FIG. 20 (1511). Costochondral junction from a 5 month old emaciated premature weighing 1800 grams at birth. Had received 3330 units vitamin D daily for 32 days. Rickets, acute severe, no healing.

FIG. 21 (1348). Costochondral junction from a 5 month old well nourished premature weighing 1600 grams at birth. Death occurred from pneumonia. Had received 3330 units vitamin D daily all its life. Rickets, subacute moderate, no healing.

FIG. 22 (1081). Costochondral junction from a 3 month old fairly well nourished premature weighing 1400 grams at birth. Death occurred from sepsis of 2 weeks duration. Had received vitamin D 3330 units daily all its life. Rickets, subacute severe; no healing.

FIG. 23 (897). Costochondral junction from a 3 month old fairly well nourished premature weighing 1950 grams at birth. Had received 6660 units vitamin D daily for 23 days. Rickets, subacute severe; no healing.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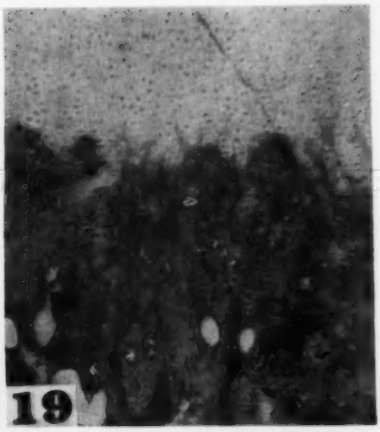
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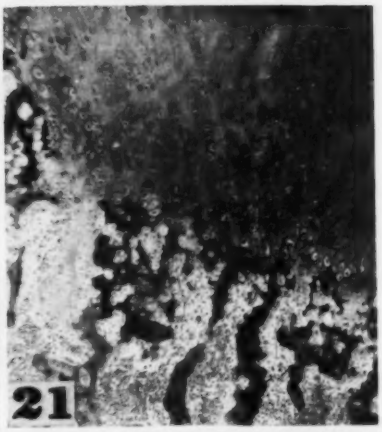
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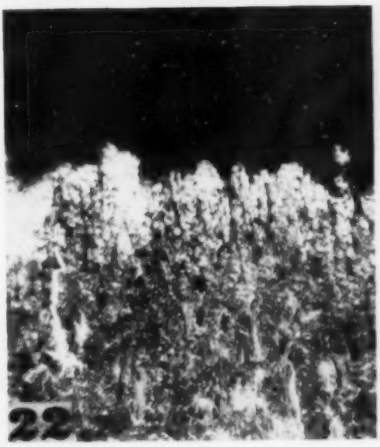
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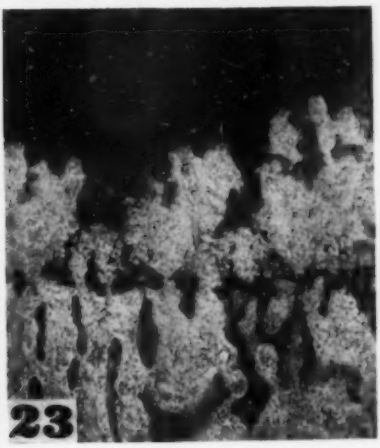
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THE JOHNS HOPKINS MEDICAL SOCIETY

Hurd Memorial Hall

MARCH 9, 1953

(The meeting opened at 8:30 p.m.)

Dr. Jonas Friedenwald: The first paper on this evening's program is by Dr. Manfred Mayer.

STUDIES ON THE MECHANISM OF HEMOLYSIS BY ANTIBODY AND COMPLEMENT

Recent advances in understanding the mechanism of lysis of sheep erythrocytes by rabbit antibody and guinea pig complement have emerged from studies of the role of Ca^{++} and Mg^{++}. It has been found that both of these cations are necessary in the hemolytic reaction. Furthermore, Ca^{++}, but not Mg^{++}, functions in the fixation of complement by antigen-antibody systems. Kinetic analyses dealing with the duration of the lag period indicate that the action of complement on the sensitized erythrocyte takes place in at least 2 successive steps, namely a reaction step requiring Ca^{++} followed by a reaction step requiring Mg^{++}.

These reaction steps are followed by a process, which we have termed the L-reaction step, and which appears to be the lytic reaction proper. The L-step is characterized by the fact that it does not involve participation of constituents of the fluid phase, it has no specific cation requirement, and it displays a rather low temperature coefficient (Q_{10} about 1.5). In a hemolytic system containing excess antibody and limited complement, the L-step requires about 2 to 3 minutes per cell. The physical or chemical nature of the L-step is not understood at present, except that it appears to involve changes within the cell membrane which lead to the release of hemoglobin, i.e., lysis proper.

Dr. Thomas B. Turner: Mr. President. It is obvious that Dr. Mayer is studying in a fundamental way a reaction with which we have been familiar for a great many years. What is not so obvious is that in the interaction between antigen and antibody and complement, it is the latter element which is the great unknown in the reaction.

Moreover, complement is a natural host component which is more or less independent of the production of antibody in response to a specific antigen. It is another expression of the individuality of the person, and we are coming to realize that these so-called non-specific host factors may play an important role in the response of the individuals to infections and other biologic insults.

I am under no obligation to interpret Dr. Mayer's findings in terms of some practical problem; suffice it to say that the more we know about these reactions, particularly as they occur *in vivo*, the more likelihood there is that they can be artificially enhanced, suppressed or altered to the benefit of the host.

Dr. Friedenwald: Any further discussion?

Dr. Frederik B. Bang: Is it possible that there are two separate reactions in which calcium is necessary for one and magnesium for the other and that both are necessary for hemolysis?

Dr. Mayer: The evidence is based on the decrease in the duration of the lag period, when the system is allowed to run through the calcium step and when timing is started upon the

addition of magnesium. This is the reason why we think the reaction sequence is the calcium step followed by the magnesium step.

Dr. George Mirick: I would like to ask a question too. I believe Dr. Mayer implied that the last reaction or the "L" reaction he described, required a measurable amount of time for its completion. I was wondering whether the length of time bore a direct relationship to the number of damaged cells?

Dr. Mayer: I actually brought three slides along to show some of the properties of this "L" reaction, but I saw that my time was running out, and I decided not to show them. The question you ask, is difficult to answer. On the basis of very limited evidence, I would say that with more damaged sites, the "L" reaction takes less time, but this is a very tentative answer. We have very few experiments on this question.

Dr. Friedenwald: Any further discussion? It is my privilege to present the next paper. I will dispense with an introduction and give you an apology instead. Last year, Dr. Moshe Wolman from the University of Jerusalem spent several months working in my laboratory in this field of histochemistry, and we worked together on the problem which will be presented tonight. Unfortunately, Dr. Wolman has gone home; consequently I am making the report in his behalf.

(Dr. Friedenwald delivered the second paper)

THE SITE OF ACID SECRETION IN THE GASTRIC MUCOSA. A HISTOCHEMICAL STUDY

The stomach of well-fasted frogs, suspended in amphibian Ringer-glucose solution, aerated with 95% O_2-5%CO_2 can be induced to secrete acid on addition of histamine to the bathing fluid. In order to reveal the site of acid secretion sodium stearate or urate was added to the bathing fluid since the free acids of these salts are quite insoluble and would be precipitated at the sites of acid production. After the experimental run, the tissues were fixed in the presence of lead acetate, converting the deposits of the test acids into lead salts. Calcium or magnesium salts were added to the fixing solution since these ions were found to diminish greatly the non-specific uptake of lead by the tissues. After embedding, sectioning and washing, the lead deposits were converted to lead sulfide by exposure to ammonium sulfide.

Under appropriate conditions non-secreting controls in the absence of histamine, and secreting or non-secreting controls in the absence of urates or stearates showed minimal deposits of lead sulfide. In the actively secreting organs exposed to the test anions, heavy deposits were found in the cytoplasm of the neck cells of the gastric glands and in the ducts of these glands. The deposits of uric acid could also be identified in the same locations as doubly refractile crystals when viewed with the polarizing microscope.

(Dr. Philip Wagley was asked to preside over the meeting at this point.)

Dr. Wagley: Are there any comments on this paper?

Dr. Lay Martin: As you know, a great deal of experimentation has taken place in the past to find the locale of hydrochloric acid formation in the stomach. As I remember, Bensley with dye methods was able to demonstrate it was in the ducts and, at times, he thought it was in the canaliculi of the parietal cell. He was never quite happy about the definiteness of this test's conclusion. Some years later some Scandinavian investigators who are well known and of whom I remember only one (Linderstrom-Lang and associates) made a most ingenious approach to the subject. They spread out animal stomachs which were fresh and with corers, like very small apple corers, removed small bites at frequent intervals from

pylorus to cardia. These small bites were fixed and sectioned transversely. They were then stained in various methods or they were subjected to various enzyme activity reactions. The investigators demonstrated with reasonable exactness that hydrochloric acid was found in the fundus and in that level of the core which corresponded with the presence of most of the parietal cells. A few years later Gersh, by rapid freezing, practically *in vitro*, soon after removal and staining, stated that he could find no chlorides in the parietal cells. Lison corroborated his work. And so the problem lay. Obviously, other studies have been reported which I either do not remember at the present time or do not know. Then, comes tonight Dr. Friedenwald's report. Everybody has always thought that hydrochloric acid was formed in the parietal cells. How is it done, by what method chloride reaches these cells, whether chloride or hydrochloric acid is stored therein—are still moot questions. However, if the speaker's conclusions are corroborated in mammalian stomach, which I think may be done, his explanation may be a solution to the problem.

Dr. Wagley: Any further comments?

Dr. Friedenwald: The next paper is by Dr. Francis Chinard.

CAPILLARY PERMEABILITY

There are two hypotheses current on the mechanism of passage of substances across capillary walls. The most widely held hypothesis is that passage occurs by filtration in bulk: a protein-free fluid with the composition of an ultra-filtrate of plasma passes through discrete pores without separation of any of the constituents of the fluid. Diffusion effects are considered to be negligible. A minority holds that diffusion is the mechanism: passage of a given substance occurs particle by particle in the direction of the gradient of its chemical potential in the case of a neutral substance and in the direction of the gradient of its electrochemical potential in the case of an ion.

The experimental approach used in the present studies, carried out at first in collaboration with Dr. Louis B. Flexner and Dr. Gilbert J. Vosburgh and more recently in collaboration with Dr. Theodore Enns, has been as follows. A solution is made of substances of different molecular weights, and hence of different diffusion coefficients, in known concentrations; an aliquot is injected "instantaneously" into the main blood vessel to an organ or region and blood is sampled at intervals of 0.3 to 3 seconds from the main blood vessel from that organ or region. The blood samples are then analyzed for the substances injected. If bulk loss occurs, i.e., if there is filtration, there should be equal loss regardless of molecular weights and of diffusion coefficients. If passage occurs by diffusion then the higher molecular weight substances with the smaller diffusion coefficients should be present in the emerging blood in higher concentration than the smaller molecular weight substances with the higher diffusion coefficients. In other words a greater fraction of the smaller substances should be lost than of the larger substances. As shown by experiments in the lungs, passage through a capillary network in itself does not result in significant separation of the substances injected though the slightly faster rate of passage of the red cells than of the plasma can be demonstrated. In a typical experiment on the hind leg of the dog, for example, the loss of inulin relative to the blue dye T-1824 (assumed not to leave the circulation in significant amount) is least, while the loss of ferrocyanide is greater, and the loss of xylose, of smallest molecular weight, is greatest of all. Loss of thiocyanate, greater in amount than the loss of inulin, occurs even in the presence of a net movement of water in the opposite direction (i.e., from interstitial spaces to blood) as brought about by the injection of concentrated human plasma albumin. Experiments have also been carried out with isotopes. Net passage of thiocyanate and of deuterium oxide from blood to interstitial spaces occurs in the presence of net move-

ment of H_2O in the opposite direction as brought about by the injection of deuterium oxide in approximately 75 per cent concentration. No differences in the net losses of deuterium oxide and of tritiated water can be demonstrated; it is concluded that in the physical process of passage across capillary walls deuterium oxide can be used as a tracer for tritium oxide and that therefore deuterium oxide can be used as a tracer for H_2O.

The net loss of H_2O in one experiment on the hind leg is calculated to be 44 per cent and that of radioactive chloride (Cl^{36}) 23 per cent of the amount injected; the ratio of the losses is approximately 1.9 compared to the ratio of the diffusion coefficients of 1.74. The diffusion hypothesis is compatible with these results while the filtration hypothesis is not. Calculation indicates that, at the very least, one-half the water in the blood stream is exchanged per minute (i.e., in man at least 2.5 liters per minute) in approximate agreement with the earlier calculation of Flexner, Vosburgh and Cowie.

A thermodynamic formulation for the rate of formation of glomerular fluid (GFR) and the applicability of the diffusion hypothesis were examined in some detail (see Am. J. Physiol., **171**, 578 (1952)). The limitations of classical formulations of GFR and of Fick's law as an adequate description of diffusion were pointed out. On the basis of the diffusion hypothesis the total glomerular surface area in both kidneys is calculated to be 2 square meters for adult man compared to the value of 1.6 square meters calculated by Vimtrup. The total peritubular capillary surface area is calculated to be about 53 square meters compared to other estimates of 23 to 45 square meters.

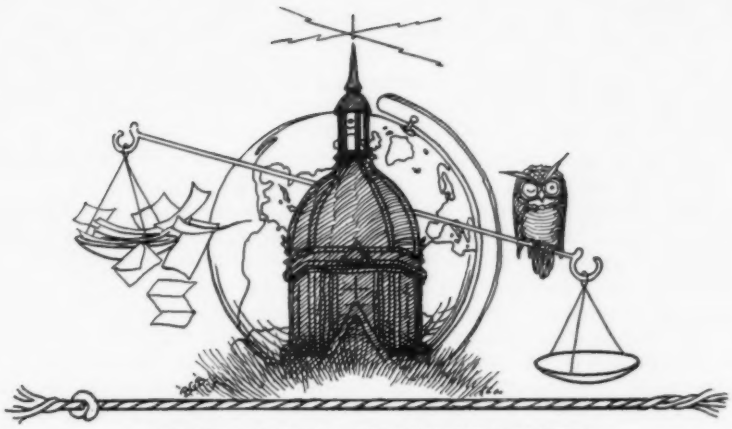
It is concluded that the hypothesis of bulk filtration through pores is not compatible with the experimental data and that the diffusion hypothesis is valid as a working hypothesis subject to more detailed experimental test. If the diffusion hypothesis is valid it appears that most of the capillary surface area is involved in the passage of water; this is in contrast to the currently held hypothesis that passage of water is restricted to discrete pores limited in distribution to the intercellular cement substance.

Dr. Friedenwald: Is there any discussion of Dr. Chinard's paper?

Dr. Albert Lehninger: I can hardly discuss this with any competence, but I would merely like to say, "Long live the minority."

Dr. Friedenwald: There being no further discussion, the meeting is adjourned.

(The meeting adjourned at 10:10 p.m.)



BOOK REVIEW

(These reviews represent the individual opinions of the reviewers and not necessarily those of the members of the Editorial Board of the Bulletin)

Hypersplenism and Surgery of the Spleen. By WILLIAM DAMESHEK AND C. STUART WELCH 84 pp., $10.00. Grune & Stratton, New York.

This revised edition of a volume originally published in 1948 consists of a series of reproductions of charts and figures which comprised an exhibit displayed at the annual meeting of the American Medical Association in 1951. The normal anatomy and physiology of the spleen, disease and dysfunction of the spleen in relation to disorders of the blood, and indications and techniques for performing splenectomy are presented in abbreviated outline form. The text is limited to the quarter-inch lettering on the charts and the presentation is therefore sketchy. Nevertheless, a broad subject matter is covered, together with the authors' concepts and theories concerning the role of the spleen in certain disease states. The method of presentation leads to a considerable amount of dogmatism and does not permit critical discussion of controversial issues. Thus the "splenic hormones" of Ungar are described as if there were no question about the existence or nature of these substances. The classical observations of Barcroft on the reservoir function of the spleen are described without reference to the fact that the studies were performed on animals and that the normal human spleen does not have a comparable contractile activity. The bibliography is largely limited to references to papers previously published by the authors.

C. LOCKARD CONLEY

Current Therapy 1953. Edited by HOWARD F. CONN. 835 pp., $11.00. W. B. Saunders Co., Philadelphia, Pa.

This is the latest in a series of such yearly publications begun in 1949 for the purpose of bringing to the practicing physician a concise up-to-date summary of accepted regimens of treatment of a wide variety of diseases. There are 209 new contributors participating in this issue and the high quality of previous years has been maintained.

Each new issue attempts to include recent developments which are of real value as opposed to purely experimental means of treatment. But in those fields in which little advance has been made, coverage by new contributors often gives new information. Thus, reference

to two or more recent issues often increases the usefulness of the series. The series is of greatest value to those such as the general practitioner or medical student, who wish a relatively brief coverage of the entire field of therapeutics.

ROBERT E. MASON

Die Gesunde und die Kranke Wirbelsäule in Röntgenbild und Klinik. (The Normal and Diseased Spine in its Clinical and Roentgenologic Aspects). By GEORG SCHMORL. Edited by Herbert Junghanns. 304 pp., Ganzleinen DM 72. (about $17.00). Georg Thieme Verlag, Stuttgart, Germany.

As one might expect from the tabulation of an experience based on some ten thousand spines examined at autopsy, this classic work represents what might be called the only existing "encyclopedia of the vertebral column." The late author's personal experience was so vast that he was able to offer in this, his *magnum opus*, beautifully illustrated examples of congenital anomalies, trauma, metabolic abnormalities, arthritides, infections and tumors affecting the vertebrae. In addition there is an excellent section on abnormalities of the intervertebral discs.

Most of the illustrations represent spines cut sagittally and photographed, x-rayed or both. There are many line-drawings, as well. The reproductions are, as is usual with this publisher, superb.

Despite the title, the bulk of the text is devoted to the diseased spine. There is almost no mention of therapy, the author being content to limit himself to descriptions of gross and microscopic pathology. Textual treatment is brief but complete and there is due mention of the pertinent literature.

Orthopedist, neurosurgeon and radiologist will find this work of special interest. Though a knowledge of German is necessary for getting along in the text, the work may be regarded as an illustrated atlas, and, as such, has no little value for the reproductions alone. Only a rudimentary familiarity with the language is needed for comprehension of the descriptions accompanying the illustrations.

DANIEL J. TORRANCE

Osteosklerose und Knochenmarkfibrose. By RUDOLF STODTMEISTER, STEFAN SANDKÜHLER AND ALBERT LAUR. 135 pp., Ganzleinen DM 28.50. Georg Thieme Verlag, Stuttgart, Germany.

This monograph of 135 pages deals with certain diseases of skeletal tissues characterized by increased bone density. The main syndromes considered are: Marble bone disease; periosteal hyperostosis; osteosclerosis associated with elementary phosphorus, lead or fluoride intoxication, and osteomyelosclerosis. There is also a section dealing with bone marrow fibrosis. Included are case reports and a bibliography of over 450 titles. The illustrations of photomicrographs and of X-rays are good, although the latter are positive prints. One can find no criticism of this volume which should prove useful to the specialist in bone diseases or hematology.

R. H. FOLLIS, JR.

Genetics and Disease. By TAGE KEMP. 330 pp., Kr. (bound) 30.00. Ednar Munksgaard, Ltd., Copenhagen, Denmark.

New medical textbooks may be judged in part by comparison with existing treatises on the same subject. The two other leading full-dress treatments (in English) of human and medical genetics which have appeared in the last few years are Gates' encyclopedic, two-volume *Human Genetics* (1946) and Stern's well-written and thorough *Principles of Human*

Genetics (1949). The object of this review was written by a physician, the Professor of Human Genetics in the University of Copenhagen. It is a welcome newcomer to the small group of texts and reference books on the subject. To the physician who is not primarily concerned with genetics Kemp's book has much to recommend it. The first parts of the book present the basic principles of genetics, particularly human genetics; later sections systematically cover various diseases about which genetic information is available.

This type of organization will, to the physician, probably be preferable to the method of using hereditary diseases mainly to illustrate principles of human inheritance (Stern). Its size will be preferred to the less wieldy dimensions of Gates' work. As in many translations of scientific writings, there are occasional unfortunate choices of words and a rare misspelling. These do not significantly detract, however, from the over-all excellence of the book.

VICTOR A. MCKUSICK

Attaining Manhood, Second Edition Revised and Enlarged. By GEORGE W. CORNER. 97 pp., $1.50. Harper and Brothers, New York.

Attaining Womanhood, Second Edition Revised and Enlarged. By GEORGE W. CORNER. 112 pp., $1.50. Harper and Brothers, New York.

Dr. Corner, who is director of the Department of Embryology of the Carnegie Institute of Washington, states in the preface to each of these books that they are written for "the intelligent boy (girl) of high school age. . . . The reason for writing separate books for boys and girls is simply that there are several phases of the subject of greater interest to one sex than to the other. There are, however, no secrets between sexes in these matters. . . ." As might be anticipated from an authority of Dr. Corner's preeminence, the sections on comparative anatomy, embryogenesis and physiology are clearly stated and impeccably correct. (There is one error, probably missed in proof, on page 20 of "Attaining Manhood" where it is stated that there "may be as many as 2,000,000 sperm cells" per ejaculum, a figure about a hundred times too small.) In the area of adolescent sex behavior, where so much remains controversial, the author is on less certain ground; there are some who would question the usefulness of the concept of "self-control" in a discussion of masturbation. In the well-adjusted adolescent, consciously exerted restraint is unnecessary; in the maladjusted, it is no solution. Too, the injunction against necking and petting seems somewhat unrealistic in view of the prevalence of these practices among adolescents. But, in general, the books are admirably designed for the healthy, intelligent high school student for whom they are intended. Dr. Corner emphasizes the beauty and poetry of sexual life, an aspect too often neglected in biological accounts. If we cavil a bit at so sharply dichotomizing the "animal" and the "mental" aspects, we are indebted to him for his presentation of their intimate relationship. If all adolescents were familiar with the information in these two well-illustrated and attractive monographs, we would be assured of a sexually healthier generation.

LEON EISENBERG

BOOKS RECEIVED FOR REVIEW

Besinnung und Bewusstsein. By G. E. STÖRRING. 134 pp., kartoniert DM 11. Georg Thieme Verlag, Stuttgart, Germany.

Das Ulkus des Magens und Zwölffingerdarms. Als Problem eines Schutzstoffmangels. By H. RAMB. 68 pp., kart. DM 6.50. Georg Thieme Verlag, Stuttgart, Germany.

Die Zusammenarbeit des Geburtshelfers, des Kinderarztes und des Serologen Bei der Prophylaxe und Therapie der Neugeborenen-Erythroblastose. By P. DAHR, K. H.

SCHÄFER and A. STADTMULLER. 64 pp., kartoniert DM 5.70. Georg Thieme Verlag, Stuttgart, Germany.

Ergebnisse der Gesamten Tuberkuloseforschung. By H. BEITZKE, ST. ENGEL, L. HEILMEYER and J. HEIN. 528 pp., Ganzleinen DM 66. Georg Thieme Verlag, Stuttgart, Germany.

Group Psychotherapy. Studies in Methodology of Research and Therapy. Report of a Group Psychotherapy Research Project of the U. S. Veterans Administration. By FLORENCE B. POWDERMAKER and JEROME D. FRANK. 615 pp., $6.50. Harvard University Press, Cambridge, Mass.

Hormonal and Neurogenic Cardiovascular Disorders. By WILHELM RAAB. 722 pp., $15.00. The Williams & Wilkins Co., Baltimore, Md.

Klinische Fehldiagnosen. By M. BURGER. 481 pp., Ganzleinen DM 58.50. Georg Thieme Verlag, Stuttgart, Germany.

Klinische Vorlesungen. By WALTER STOECKEL. 74 pp., kart. DM 5.70. Georg Thieme Verlag, Stuttgart, Germany.

Leitfaden der Neurologie. By F. LAUBENTHAL. 291 pp., Ganzleinen DM 28. Georg Thieme Verlag, Stuttgart, Germany.

Liver Injury. Transactions of the Eleventh Conference, April 30 and May 1, 1952. Edited by F. W. HOFFBAUER. 265 pp., $4.00. The Josiah Macy, Jr. Foundation, New York.

Modern Treatment. A Guide for General Practice. By Fifty-three Authors. Edited by AUSTIN SMITH and PAUL L. WERMER. 1146 pp., $20.00. Paul B. Hoeber, Inc., New York.

Plastic Surgery at The New York Hospital One Hundred Years Ago. With Biographical Notes on Gurdon Buck. By HERBERT CONWAY and RICHARD B. STARK. Forewords by JOHN HAY WHITNEY, STANHOPE BAYNE-JONES and FRANK GLENN. 110 pp., $5.00. Paul B. Hoeber, Inc., New York.

Problems of Infancy and Childhood. Transactions of the Sixth Conference March 17 and 18, 1952. Edited by MILTON J. E. SENN. 160 pp., $2.50. The Josiah Macy, Jr. Foundation, New York.

Sexual Harmony in Marriage. By OLIVER M. BUTTERFIELD. Introduction by Nadina Kavinoky. 96 pp., $1.50. Emerson Books, New York.

Technik der Blutgruppen-und Blutfaktoren-Bestimmung. By PETER DAHR. 320 pp., Ganzleinen DM 24. Georg Thieme Verlag, Stuttgart, Germany.

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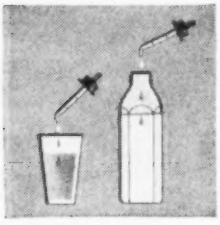

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